Diabetic Kidney Disease: Comprehensive Management Overview

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Diabetic Kidney Disease: Comprehensive Management Overview

Learning Objectives

By the end of this handout, students will be able to: 1. Understand the pathophysiology and clinical manifestations of diabetic kidney disease (DKD) 2. Compare the efficacy of RAAS inhibitors, SGLT2 inhibitors, finerenone, and GLP-1 receptor agonists 3. Apply evidence-based sequencing of medications for DKD management 4. Identify appropriate candidates for each drug class and manage side effects 5. Calculate number needed to treat (NNT) and communicate outcomes to patients

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Epidemiology & Pathophysiology

DKD Burden

- **Leading cause** of chronic kidney disease globally (affects ~40% of diabetic patients)
- **537 million** individuals with diabetes worldwide
- **Mortality:** 30-40% 5-year mortality rate (cardiovascular disease #1 cause)

Mechanisms of Kidney Injury

1. **Glomerular hyperfiltration** ☐ intraglomerular pressure elevation
2. **Inflammation** ☐ cytokine activation, immune cell infiltration
3. **Fibrosis** ☐ TGF-β activation, myofibroblast proliferation
4. **Tubular dysfunction** ☐ impaired sodium/glucose reabsorption
5. **Metabolic dysfunction** ☐ mitochondrial injury, oxidative stress

Key Point: DKD is multifactorial; single-agent therapy insufficient for optimal outcomes.

Four Pillars of DKD Therapy

Pillar 1: RAAS Inhibition (ACE-I/ARBs)

Comparative Efficacy Table

Parameter	ACE Inhibitors	ARBs	Clinical Significance
Kidney failure prevention	39% reduction (RR 0.61)	18% reduction (RR 0.82)	ACE-I superior
All-cause mortality	22% reduction*	No benefit	ACE-I advantage
Doubling SCr prevention	42% reduction	21% reduction	ACE-I better
Albuminuria reduction	25-35%	25-35%	Similar
Hyperkalemia risk	3.4% absolute ☐	3.9% absolute ☐	Similar
Cough incidence	10-15%	<1%	ARB better tolerated
NNT for kidney failure prevention	67	—	Modest benefit

*Only at maximally tolerated doses

Key Insights

- **Both are foundational,** but ACE-I shows slight edge in mortality when dosed optimally
- **Direct comparisons show minimal difference** between ACE-I and ARBs
- **Uptitration critical:** Full-dose therapy required; many patients undertreated
- **Implementation gap:** Only 17% of eligible CKD patients initiated RAAS blockade within 1 year of diagnosis

Pillar 2: SGLT2 Inhibitors — Paradigm Shift

Major Trials Summary

Trial	n	Population	Primary Outcome RRR	NNT	Key Secondary
CREDENCE (Canagliflozin)	4,401	T2DM + CKD stages 2-3	30% kidney/CV composite	23	32% ESKD reduction; 31% CV death/HHF
DAPA-CKD (Da-pagliflozin)	4,304	CKD ± T2DM	39% kidney/CV composite	19	46% eGFR ≥50% decline; 31% mortality
EMPA-KIDNEY (Em-pagliflozin)	6,609	CKD ± T2DM	28% kidney/CV composite	26	29% progression; 14% hospital-ization

Meta-Analysis: 13 Trials, 90,413 Participants

- **37% reduction** in kidney disease progression (HR 0.63, 95% CI 0.58-0.69)

- **Benefits across all:** CKD stages, albuminuria levels, diabetic + non-diabetic disease
- **Rapid onset:** Benefit curves separate within 3-6 months of treatment initiation
- **Albuminuria reduction:** 30-40%

Mechanisms of Renoprotection

1. Reduction in intraglomerular pressure via tubuloglomerular feedback restoration
2. Decreased tubular workload and oxygen consumption
3. Metabolic reprogramming favoring ketone utilization
4. Anti-inflammatory and anti-fibrotic effects
5. Direct natriuretic and blood pressure effects

Clinical Implementation

- **Initiate regardless of glycemic control** (not just for diabetics)
- **Start early:** Benefit appears within 3-6 months
- **Continue to eGFR 20:** Benefit demonstrated even in advanced CKD
- **Expected eGFR dip:** 3-5% decline in first weeks (benign hemodynamic change)
- **Side effect:** Genital infections (educate on hygiene; consider prophylaxis if recurrent)

Pillar 3: Non-Steroidal MRA (Finerenone)

Trial Results (FIDELITY Pooled Analysis)

Outcome	FIDELIO-DKD	FIGARO-DKD	FIDELITY Pooled
Population	Advanced CKD (eGFR 44)	Earlier CKD (eGFR 68)	Combined
Kidney outcomes reduction	18% (HR 0.82)	13% (HR 0.87)	**23% (HR 0.77)**
CV outcomes reduction	14% (HR 0.86)	13% (HR 0.87)	**14% (HR 0.86)**
Kidney failure reduction	13%	Limited	**20%**
Albuminuria reduction	31%	32%	**32%**
NNT (kidney failure)	—	—	48
Hyperkalemia ≥5.5 mmol/L	15.8% vs 7.8%	10.8% vs 5.3%	14% vs 6.9%

Unique Advantages Over Spironolactone

- More balanced tissue distribution (kidney-selective)
- Greater MR selectivity (fewer off-target effects)
- **Lower hyperkalemia risk** vs steroidal MRAs
- Anti-inflammatory and anti-fibrotic beyond hemodynamics

Critical Combination Data

- **Benefits preserved with SGLT2 inhibitors:** Interaction p=0.63 (non-significant)
- **Safe combination:** No excess hyperkalemia beyond expected from each agent
- Supports use of both agents as complementary therapies

Pillar 4: GLP-1 Receptor Agonists — Emerging Fourth Pillar

FLOW Trial: Semaglutide in DKD

Outcome	Semaglutide	Placebo	HR	ARR	NNT
Primary composite (kidney failure, ≥50% eGFR □, kidney/CV death)	18.7%	23.2%	0.76	4.5%	22
Kidney-specific composite	15.2%	18.7%	0.79	3.5%	29
CV death	5.2%	7.0%	0.71	1.8%	56
MACE (major adverse CV)	11.8%	14.0%	0.82	2.2%	45
All-cause mortality	9.0%	11.0%	0.80	2.0%	50
eGFR slope benefit	—	—	—	+1.16 mL/min/year	—
UACR reduction	—	—	—	32% greater	—

Trial Design (FLOW)

- 3,533 T2DM patients with CKD (eGFR 25-75)
- Albuminuria requirements stratified by eGFR
- Trial stopped early due to efficacy
- Benefit consistent across all CKD stages

Mechanisms of Kidney Protection

1. Direct natriuretic effects (NHE3 inhibition)
2. Anti-inflammatory actions
3. Improved glycemic control (without hypoglycemia risk)
4. Weight loss (mean 5.4 kg)
5. Blood pressure reduction
6. Direct anti-fibrotic effects

Clinical Implementation Notes

- **Preserved benefit with SGLT2i:** No interaction (p=0.755)
- **Side effects:** GI (nausea) common but manageable; no increase in serious AEs
- **Slow titration:** Improves GI tolerance
- **Cost:** Highest of four pillars (~$800-1000/month)

Biomarkers & Monitoring

Albuminuria: The Therapeutic Target

Why albuminuria matters: - Unlike heart failure (natriuretic peptide resistance), albuminuria remains modifiable throughout DKD - **30% albuminuria reduction** associated with ~23% reduction in kidney failure risk - **Target:** <30 mg/g (or 50-70% reduction from baseline)

Expected Albuminuria Reductions by Agent

- ACE-I/ARB: 25-35%
- SGLT2i: 30-40%
- Finerenone: 30-35%
- GLP-1 RA: 30-40%
- **Combination:** Can achieve >50-60% reduction

eGFR Initial "Dip" — Expected & Benign

Agent	Initial Decline	Mechanism
ACE-I/ARB	5-10%	Efferent vasodilation ☐ pressure drop
SGLT2i	3-5%	Tubuloglomerular feedback restoration
Finerenone	2-3%	Afferent vasodilation

Key Point: This dip reflects beneficial hemodynamic changes. Do NOT discontinue therapy. Long-term eGFR slopes improve dramatically with all agents.

Monitoring Schedule

- **New initiation:** Labs at 2 weeks (K☐, Cr, BP)
- **Established therapy:** Q3-6 months (K☐, Cr, eGFR slope)
- **Albuminuria:** Annually
- **HbA1c:** Q3-6 months (if on GLP-1 RA)

Optimal DKD Management: Sequencing & Targets

Step 1: Foundation Therapy (Initiate Weeks 0-4)

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├─ ACE inhibitor OR ARB (maximal tolerated dose)
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|   └─ lisinopril/enalapril: target 20–40 mg/day
|   └─ losartan/valsartan: target 80–160 mg/day
|   └─ Monitor: K⁺, Cr at 2 weeks
|
└─ Add SGLT2 inhibitor (regardless of glycemia)
    └─ empagliflozin 10 mg OR dapagliflozin 10 mg daily
    └─ canagliflozin 100 mg daily
    └─ Educate: Genital hygiene, sick-day management, volume status
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Target: Completed within 3 months of DKD diagnosis

Step 2: Risk Stratification (Weeks 12-16)

If albuminuria remains >30 mg/g: - Add finerenone 10 mg daily (start lower if eGFR <60) - Recheck K□ at 4 weeks, then q3-4 months - Accept K□ <5.5 mEq/L; hold if ≥6.0

If HbA1c >7% or high cardiovascular risk: - Add GLP-1 RA (semaglutide 0.25 mg □ titrate to 1.0 mg weekly) - Slower titration improves GI tolerance - Recheck labs at 4 weeks

Target: Complete assessment by 6 months

Step 3: Optimization (Months 6-12)

- Titrate all agents to maximally tolerated doses
- Monitor potassium closely (especially if on both RAAS blocker + finerenone)
- Track eGFR slope (should improve/stabilize)
- Reinforce adherence; address cost barriers
- **Target:** All eligible therapies at goal doses by 12 months

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Stage-Specific Approaches

Early DKD (eGFR >60, UACR 30-300 mg/g)

Priority: Primary prevention - SGLT2i critical (regardless of HbA1c) - GLP-1 RA for additional glycemic control + CV benefit - ACE-I/ARB if hypertensive or albuminuria present

Moderate DKD (eGFR 30-60, UACR >30 mg/g)

Priority: Slow progression - All four pillars indicated if tolerated - Close K□ monitoring (especially with finerenone) - Monthly BP targets <130/80 mmHg - SGLT2i continued to eGFR 20

Advanced DKD (eGFR <30)

Priority: Prepare for renal replacement therapy while slowing progression - Continue ACE-I/ARB (careful monitoring) - SGLT2i shown beneficial down to eGFR 20; continue - Limited data for finerenone + GLP-1 RA at this stage - Assess readiness for dialysis/transplant - Involve nephrology specialists

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Safety Monitoring & Side Effects

ACE-I/ARB Safety

Concern	Management
Hyperkalemia	Accept ≤30% Cr rise; K□ <5.5 = continue; dietary K□ counseling
Acute kidney injury	Expected 5-10% eGFR dip; monitor 2 weeks; discontinue if decline >30%
Angioedema (ACE-I)	Switch to ARB if occurs

SGLT2 Inhibitor Safety

Concern	Management
Genital infections	Hygiene education (wipe front-to-back); prophylactic fluconazole if recurrent
Volume depletion	Counsel on adequate hydration; hold before major surgery
Euglycemic DKA (rare)	Educate on sick-day rules; hold during acute illness

Finerenone Safety

Concern	Management
Hyperkalemia	Start 10 mg if eGFR <60; recheck K□ at 1 month; hold if ≥5.5; retry after correction
Hypotension	Monitor BP; reduce if SBP <120 persistently

GLP-1 RA Safety

Concern	Management
GI symptoms (nausea)	Slow titration; small frequent meals; antiemetic if needed
Injection site reactions	Rotate injection sites; reassure usually self-limited
Pancreatitis (very rare)	Educate on warning signs; D/C if suspected

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The Implementation Gap: Why Therapies Underused

Therapy	Eligible	Actually Receiving	Gap	Barriers
ACE-I/ARB	90%	40-70%	20-50%	Hyperkalemia fears, creatinine rise concerns, lack of uptitration
SGLT2i	80%	10-30%	50-70%	Cost, safety concerns, "diabetes drug" perception
Finerenone	60%	<5%	>90%	New therapy, hyperkalemia monitoring, cost
GLP-1 RA	70%	5-15%	55-65%	Injectable route, GI side effects, cost/access

Clinical Pearl: Implementation of existing therapies prevents more kidney failure cases than discovery of new drugs.

Cost-Effectiveness & Patient Communication

Cost Per Quality-Adjusted Life Year (QALY)

- ACE-I: **Dominant** (cheapest + most effective)
- SGLT2i: $30-50K/QALY
- Finerenone: $40-60K/QALY
- GLP-1 RA: $50-80K/QALY
- Combination therapy: Cost-effective by standard US thresholds (<$100K/QALY)

Key Messages for Patients

1. **"DKD is serious but treatable."** Modern medications can slow/stop progression.
2. **"Multiple medications work better."** Like managing hypertension, combination therapy provides better results.
3. **"Starting early matters."** Benefits appear within months, compound over years.
4. **"Expect lab dips initially."** Kidney numbers may drop slightly—this is beneficial long-term.
5. **"Regular monitoring keeps you safe."** Blood tests ensure medications work without harm.
6. **"Cost assistance exists."** Patient assistance programs available for all drug classes.

Practice Questions

Question 1: A 62-year-old with T2DM, eGFR 48, UACR 150 mg/g, and hypertension is started on lisinopril. Two weeks later: K□ 5.3, Cr increased from 1.5 to 1.8 mg/dL (27% rise). What is the most appropriate action?

A) Discontinue lisinopril immediately; switch to nifedipine
B) Continue lisinopril; this is expected; recheck labs in 4 weeks
C) Reduce lisinopril dose by half
D) Add potassium binder (sodium polystyrene sulfonate)

Answer: B — A 27% creatinine rise is within acceptable parameters (up to 30%). This reflects hemodynamic benefit, not true kidney injury. Continue therapy, recheck labs, and plan to add SGLT2i next.

Question 2: Your T2DM patient is on lisinopril 40 mg, empagliflozin 10 mg, and finerenone 20 mg, but UACR is still 120 mg/g after 6 months. HbA1c is 8.2%. What is the next step?

A) Increase finerenone to maximum dose
B) Add GLP-1 RA (semaglutide) for additional albuminuria reduction
C) Switch empagliflozin to dapagliflozin (different SGLT2i)
D) Consider kidney biopsy to reassess diagnosis

Answer: B — GLP-1 RA provides additional 30-40% albuminuria reduction and improves glycemia. Also, elevated HbA1c (8.2%) suggests benefit from GLP-1 agent.

Question 3: A 71-year-old with T2DM, CKD stage 3b, and mild albuminuria wants to avoid "too many pills." Which single agent provides the most evidence-based kidney protection in early DKD?

A) Increase lisinopril dose
B) Start SGLT2 inhibitor
C) Add finerenone
D) Start GLP-1 receptor agonist

Answer: B — SGLT2i demonstrates 37% kidney protection across all CKD stages, benefits both diabetic and non-diabetic disease, and has the largest clinical trial base. If forced to choose one agent beyond RAAS blockade, SGLT2i is the highest priority.

Summary: The Four Pillars At-A-Glance

Pillar	Mechanism	Kidney Failure RRR	NNT	Cost/Month	Uptake
RAAS-I	Hemodynamic (efferent dilation)	20-40%	67	$5-20	40-70%

Pillar	Mechanism	Kidney Failure RRR	NNT	Cost/Month	Uptake
SGLT2i	Hemodynamic + metabolic	30-40%	26	$400-500	10-30%
Finerenone	Aldosterone + inflammation	20-25%	48	$400-500	<5%
GLP-1 RA	Metabolic + hemody-namic	20-30%	22	$800-1000	5-15%

Bottom Line: Combination therapy targeting multiple mechanisms provides 50-60% reduction in kidney failure risk compared to no treatment. Optimal care requires overcoming implementation barriers and patient education.

See Also

Related Student Handouts

- CKD Overview and Classification
- CKD Complications
- CKD Nutrition and Dietary Management
- RAAS Inhibitors and Renal Protection
- SGLT2 Inhibitors in Kidney Disease
- GLP-1 Receptor Agonists and Renal Benefits

Clinical Content (01-Clinical-Medicine/Nephrology)

- CKD Hub - Full Clinical Reference
- Essential Renal Laboratory Tests

Atomic Notes (ZK)

- RAAS System and Blood Pressure Regulation

Butler-COM Resources

- Butler COM - Nephrology Deep Dive

Additional Resources

- Full Comprehensive Management Report
- KDIGO 2022 Diabetes Management in CKD Guideline
- FLOW Trial: GLP-1 Receptor Agonists in CKD

This handout emphasizes rapid, early, multi-targeted therapy as the modern standard for DKD management. The evidence base supports combination therapy with sequential addition of agents rather than traditional monotherapy approaches.